Armed Forces College of Medicine

AFCM

Nutritionally essential elements with their impacts on liver diseases

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INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

- Explain the biomedical importance of minerals
- Correlate copper metabolism to Wilson disease

What are the minerals?

-**Inorganic** elements which are **essential** nutrients.

-**Not changed** by digestion or metabolism.

Classification of minerals

Minerals are classified into 3 groups

1- Macrominerals (major elements)

- Present in great amounts in tissues.
- The daily requirements for each is>100 mg/day

EX: 7 elements

Ca , Mg , Phosphorous,

Na, K, Cl , Sulfur

2- Microminerals (trace elements)

- Present in minimal amounts in tissues
- The daily requirements for each is < 100 mg/day

EX: Iron ,Iodine ,

Copper, Cobalt , chromium, Mn

3-Extra trace elements <1 mg/day Molybdeneum , Selenium , Zn

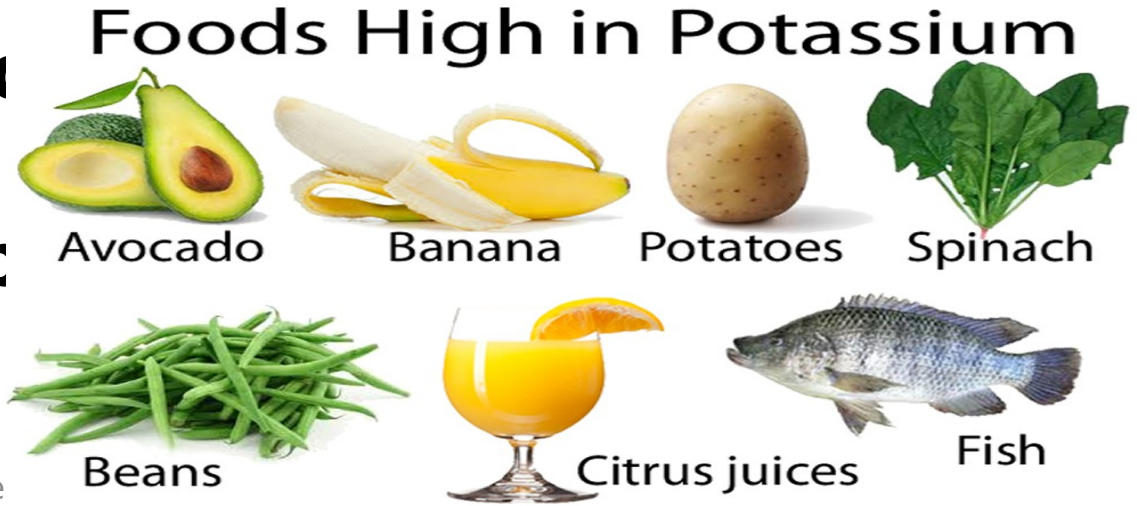
Macrominerals

1-Potassium

- 2/3 of potassium is present in tissues and body fluids (potassium is **the main intracellular cations**)
- 1/3 is present in the skeleton

Functions

1. Regulation of osmotic and acid-base balance
2. Nerve and muscle excitab
3. Normalize heart rhythms



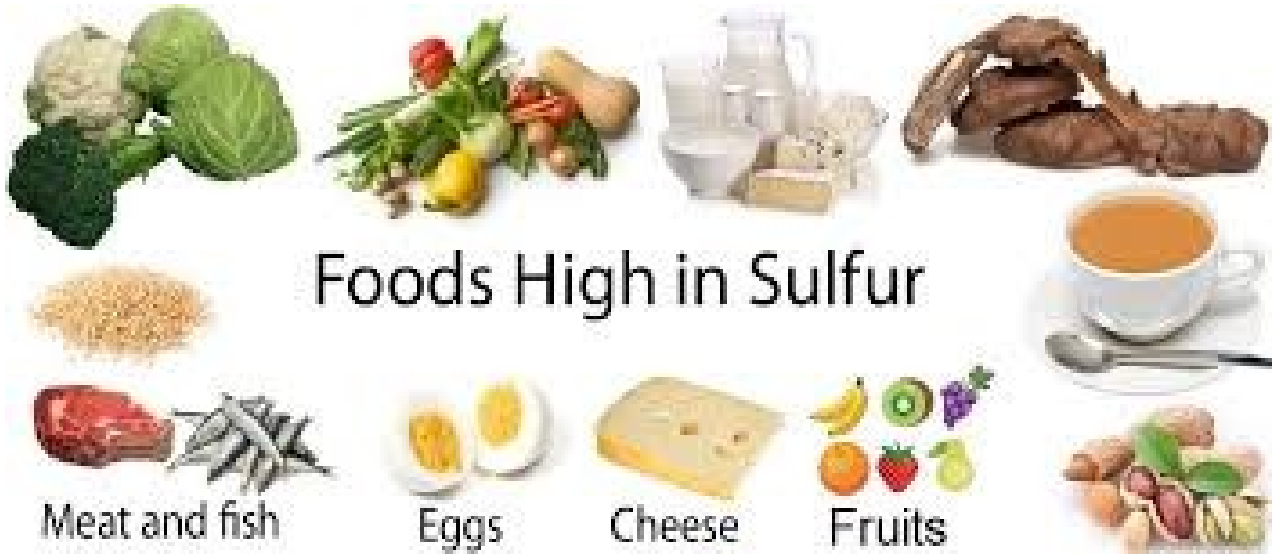
2-Magnesium

- **1-Proper nerve function & neurotransmission.**
- **2-Stabilize the APT co-substrate in enzymatic reactions.**
- **2-Regulate Muscle contraction**
- **3-Plays an important role in regulating the neuromuscular activity of the heart; maintains normal heart rhythm.**
- **Decrease magnesium level**

 tremors, poor appetite, p
nystagmus and hypomagne

3-Sulfur

1. **Enters in the formation of keratin of**
2. **Enter in structure Insulin.**
3. **The sulfur-containing amino acids (methionine, cystine, cysteine)**
4. **sulfur-containing Vitamins: biotin and thiamine**



II-Trace elements

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v3Y&ust=1569031222500633&ictx=3&uact=3

Copper metabolism

Biological functions:

Case scenario

A 15 years-old girl presented with abdominal pain and diarrhea for 3 days. She became jaundiced and provisional diagnosis of hepatitis.

#Lab. Findings :

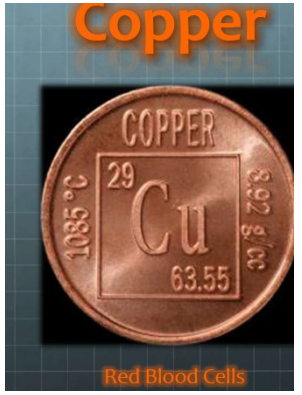
- **Increased transaminases**
- **CBC anemia and thrombocytopenia**
- **The total serum copper level was decreased**
- **The free serum copper level was increased**
- **Serum Ceruloplasmin level < 20 mg/dl decreased**
- **Urine copper excretion/24h : increased**

What is your clinical impression?

Wilson’s disease :
genetic disease
due to accumulation of large amount of copper

Genetic study revealed mutation of a gene encodending a membrane bound copper transporting ATPase

Copper



Food Sources:

- Liver & kidney , Meats
- Legumes, leafy green vegetables.
- fruits
- Nuts
- Chocolate
- Cows milk is poor sou

Normal level;

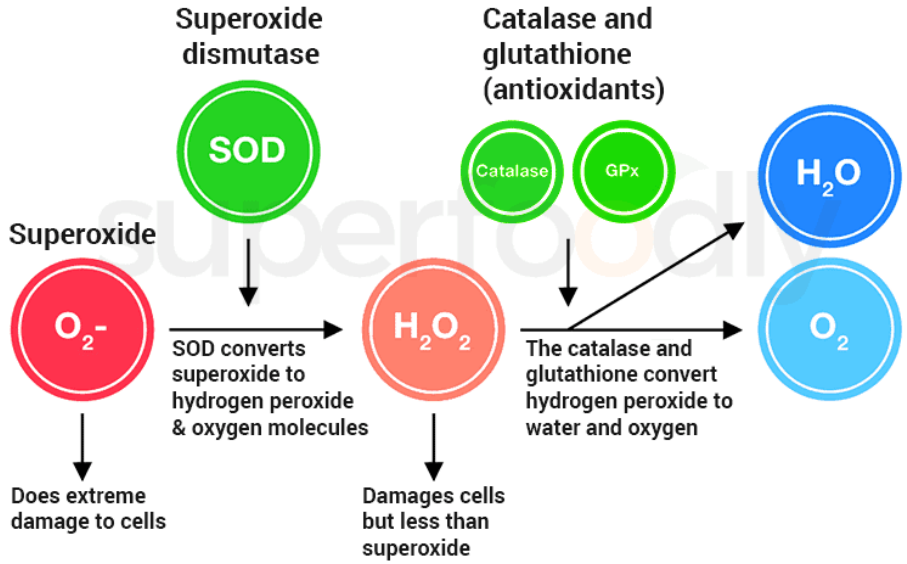
(normal serum copper 10-22 umol/L) = 100 - 200 ug/dl

Biological functions:

- **Help in iron absorption in Ferric state**
- **Hb synthesis (ALA synthase is a cu containing enzyme) (anemia)**
- **Bone formation synthesis of collagen**
- **Nervous tissue function**
- **component of many intracellular metalloenzymes**

Activity of many enzymes as:

1. **Superoxide Dismutase (SOD)**



2. **Lysyle oxidase**

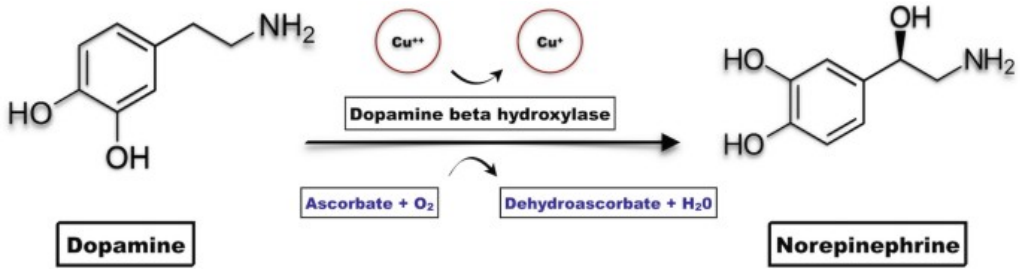
defective synthesis of collagen , defective bone and teeth , hypotonia, hyperelastisty and osteoporosis

3. **Tyrosinase (Melanine**

continue

4. Cytochrome c oxidase **lack of ATP synthesis , lethargy and weakness**

5.Ferroxidase Fe^{++} Fe^{+++}

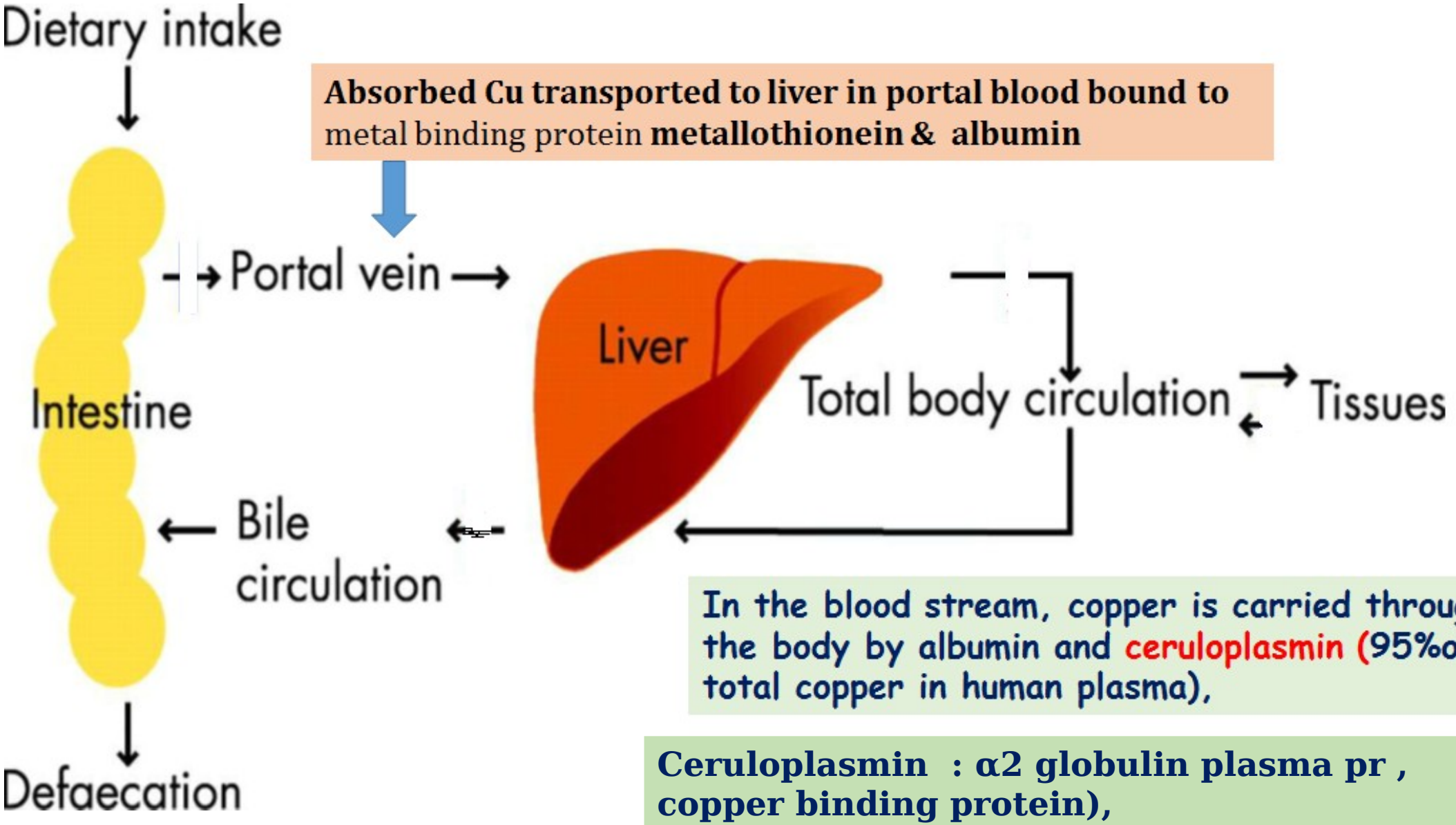


6. Dopamine b-hydroxylase

7. Desaturase

8. Monoamine oxidase

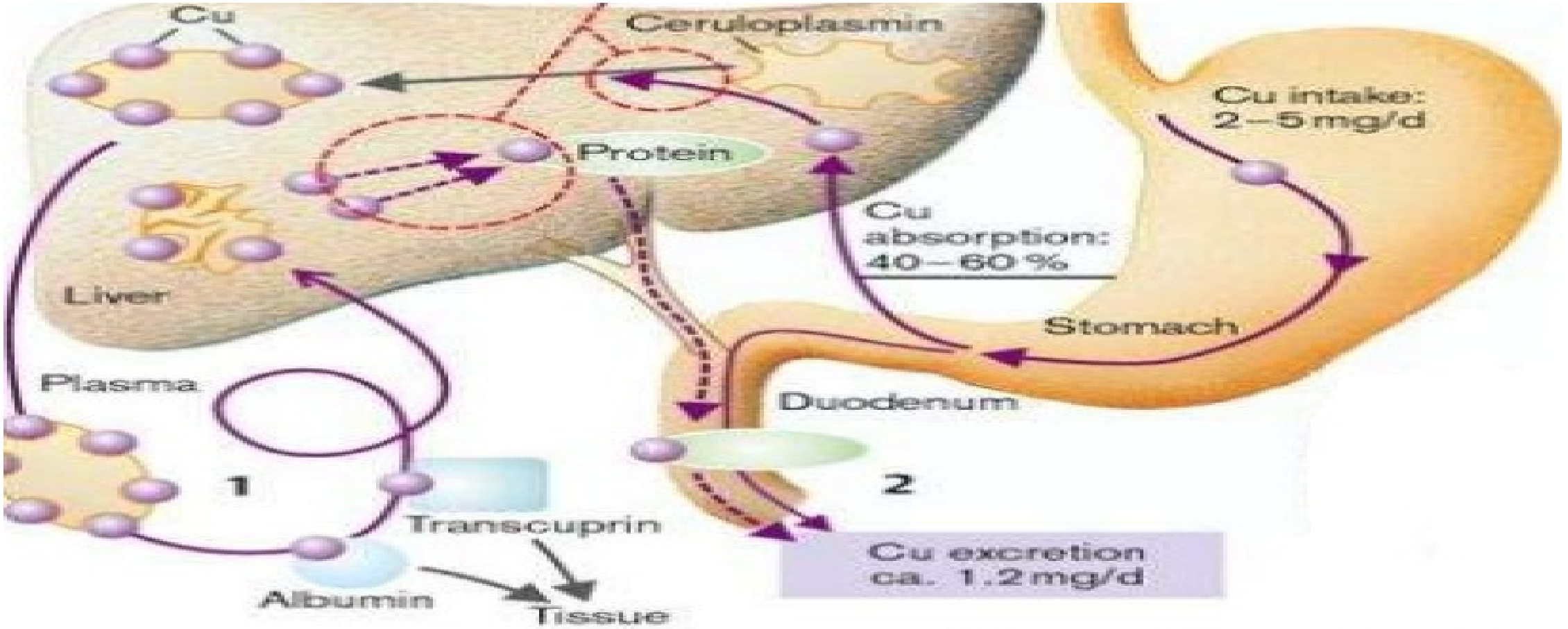
- are mitochondrial enzymes that oxidatively deaminate endogenous biogenic amine neurotransmitters such as dopamine, serotonin, norepinephrine, and epinephrine.



In the blood stream, copper is carried throughout the body by albumin and ceruloplasmin (95%of the total copper in human plasma),

Ceruloplasmin : α2 globulin plasma pr , copper binding protein),

Normal copper metabolism



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Quiz

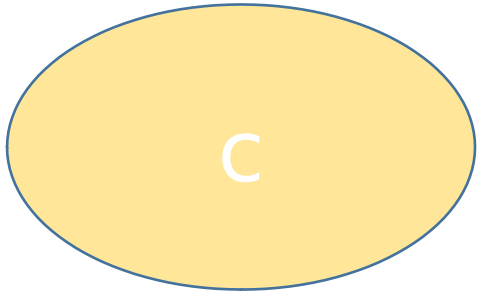
- Which is the primary route for elimination of copper from body?

a. Renal excretion

b. Liver sulphation

c. Biliary excretion

d. Sloughing of intestinal mucosal cell



Alterations of plasma copper

1-Cu Toxicity Wilson's disease(Hepatolenticular degeneration)

2-Copper Deficiency (Menks syndrome)

Alterations of plasma copper:

1-Cu Toxicity

- Dietry **:rare**
- Genetic : systemic Cu Overload
  Wilson's disease (hepatolenticular degeneration).

- **Increased serum free cu levels**
- **Decreased plasma ceruloplasmin**
- **This disease is characterized by accumulation of large amounts of**

Wilson's disease (Hepatolenticular degeneration)

➢**Cause:**

It is a genetic disease (autosomal recessive disorder),

due to mutation of ATP7B gene

encodending membrane bound copper transporting ATPase

➢**Biochemical basis of Wilson's:**

(1) Excessive copper absorption from the intestine.

(2) Failure of Copper excretion via bile.

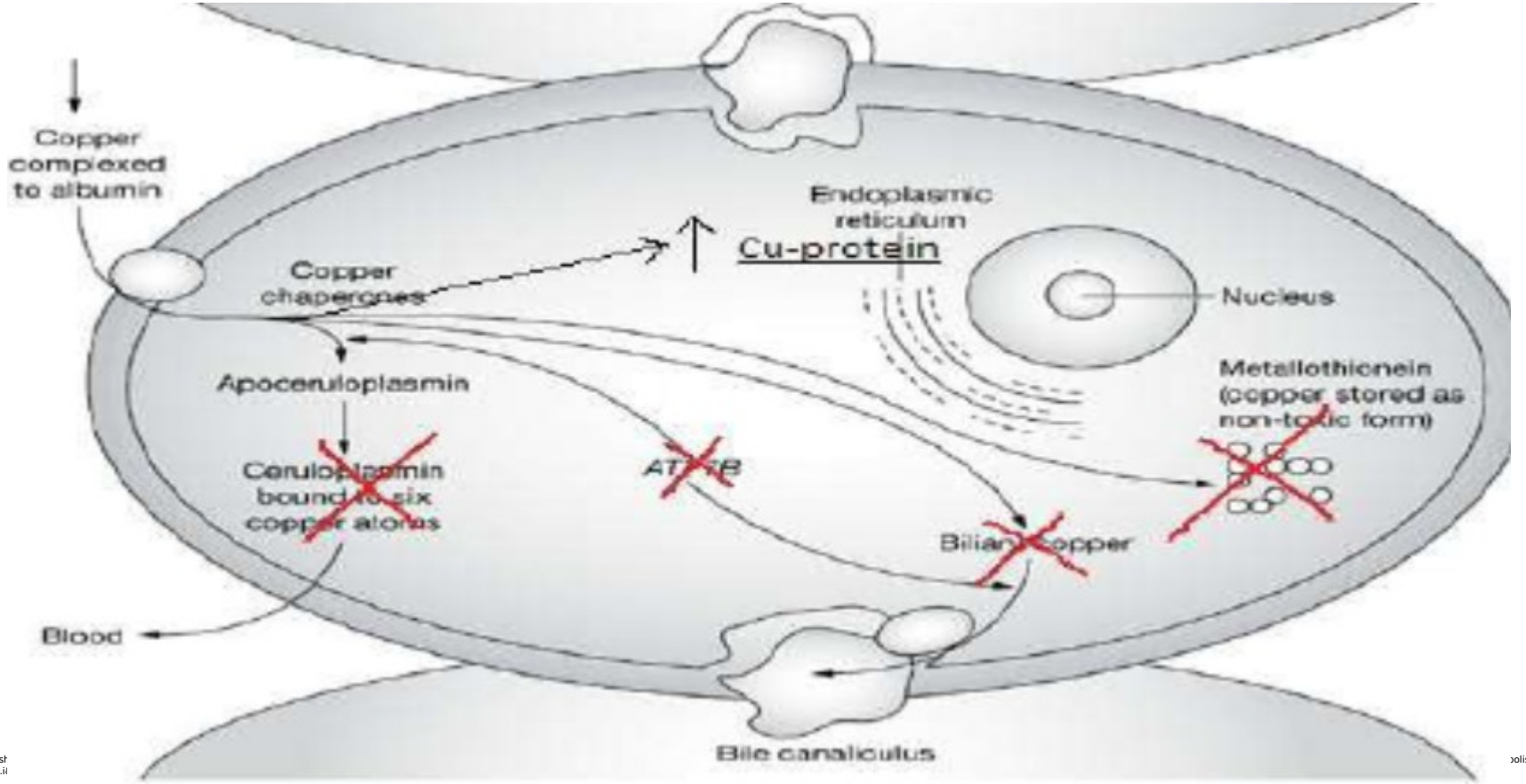
(3) Failure to synthesize ceruloplasmin (Inadequate incorporation of copper into apoceruloplasmin

➢**Clinical picture:**

It is characterized by accumulation of large amounts of copper in liver and different organs :

- **Age of onset of symptoms range from 6 to 40 years**
- **Incidence 1:30000**

Abnormal copper metabolism



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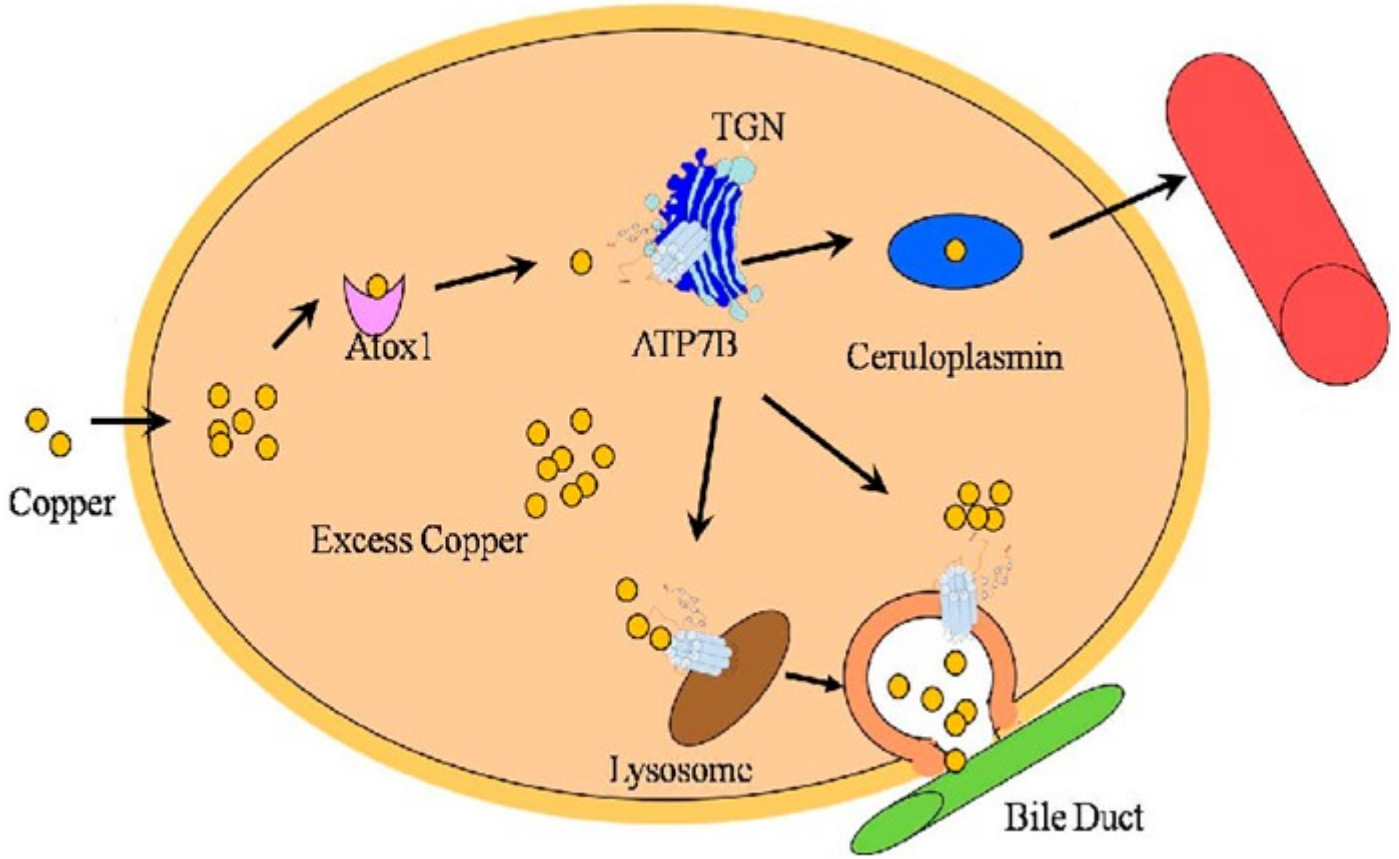
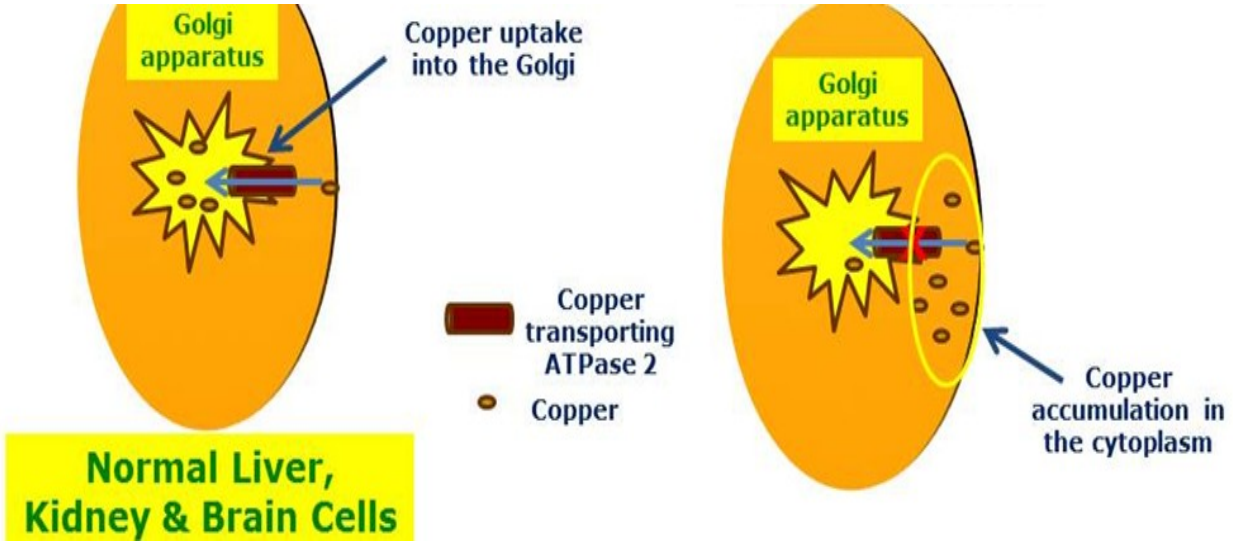
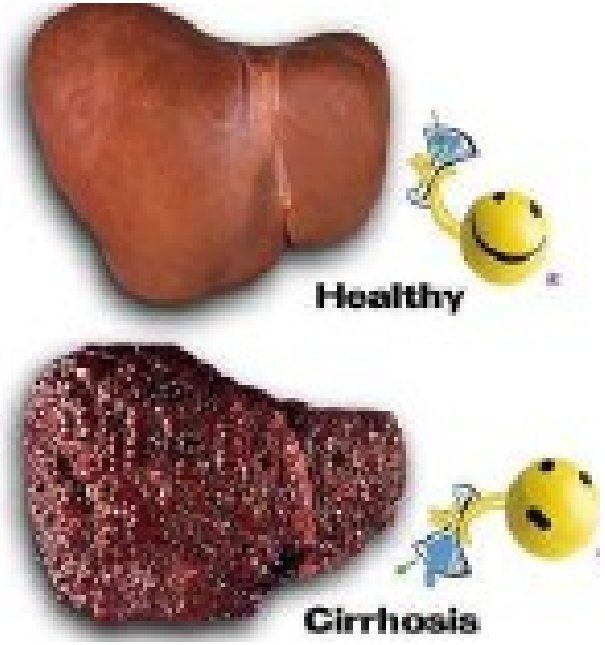


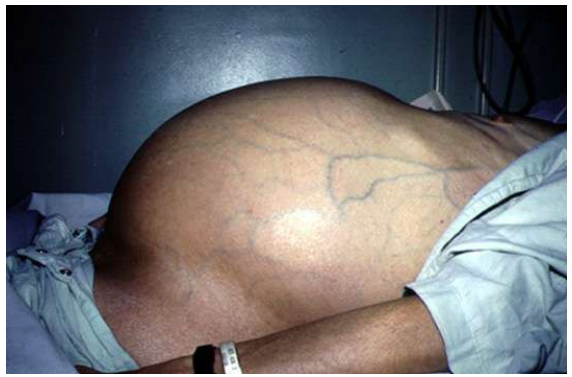


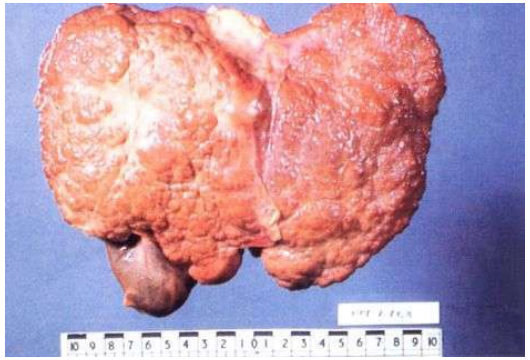
https://disorders.eyes.arizona.edu/disorders/wilson-disease

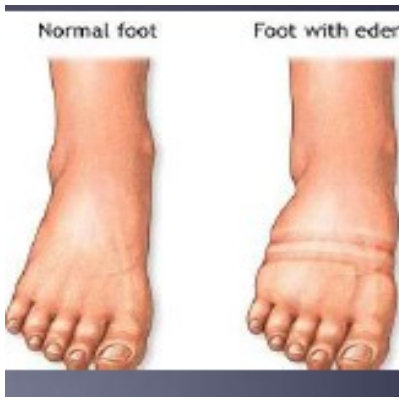
Hepatic presentations of Wilson Disease

- More common in children than in adults
- Vague symptoms & non specific Hepatitis and liver cirrhosis
- Sever hepatic failure
- Hepatic decompensation with ascites
- Peripheral edema
- Hepatic Encephalopathy









Neurological presentation

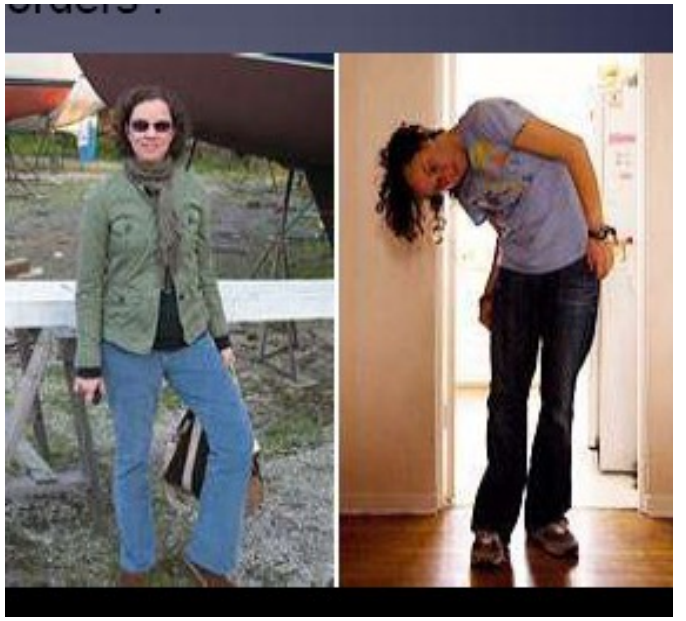
- **Tends to occur in 2nd and 3rd decades or later**
- **defective formation of myelin sheath**
- **3 main movement disorders**

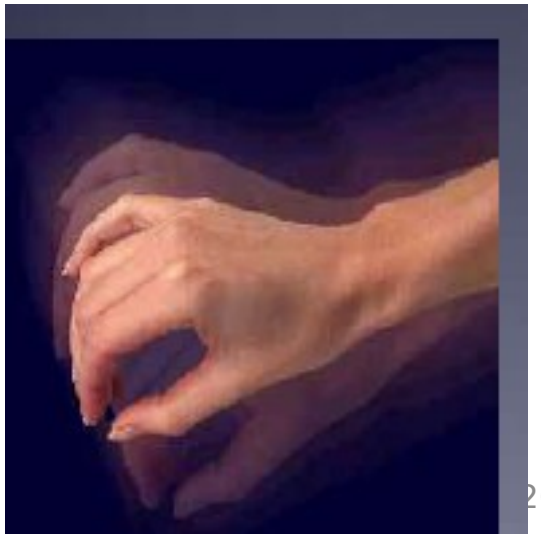
❖ **Dystonia**

❖ **Tremors**

❖ **parkinsonism**

✖ **lentiform nucleus of the brain**





Psychiatric disorders

- **20% of cases**
- **Loss of Emotional control**
- **Aggressive antisocial behavior**
- **Depression**

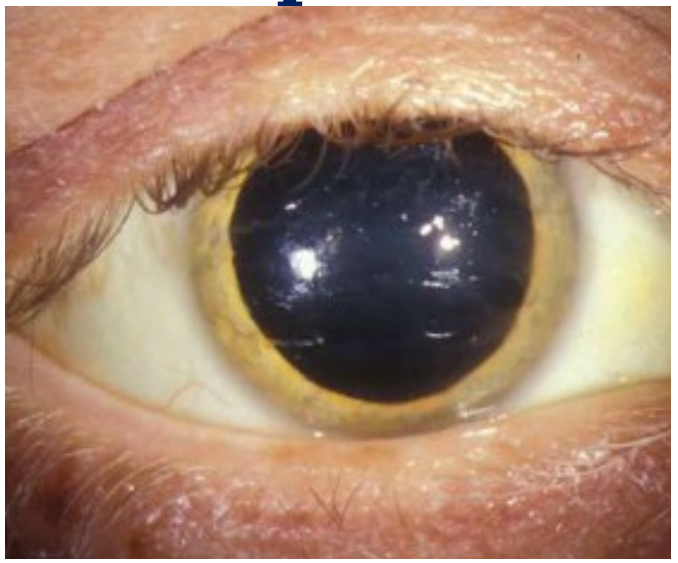
Ocular signs

Cornea green or golden pigments around the cornea

(**Keyser- Fleisher ring**)

Due to deposition of cu in basement membrane

Lense Sun flower cataract due to cu deposition in the lense



Laboratory diagnosis

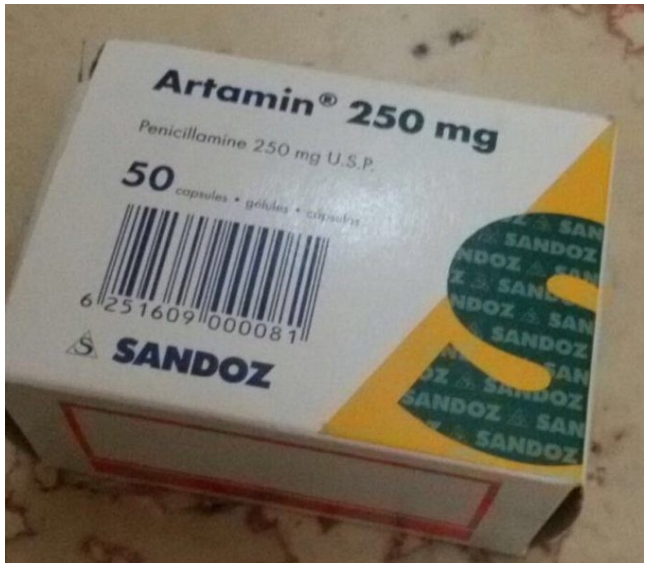
- **Low Ceruloplasmin level < 10 mg/dl**
  (N: 20-35 mg/dl)
- **High Urinary copper excretion rate >100mg/day**
  (N: 20-50 ug/24hs).
- **High Free copper level > 25 ug/dl OR >3.9 umol/L**
  (N: 8-12ug/dl = 1.3 :1.9 umol/L)
- **Low total copper level**
- **Liver biopsy : CU levels >250 ug/g of dry weight**
  (N: 20-50 ug/g of dry weight)

Treatment:

Penicillinamine:

which:

- **chelates copper**
- **and increase its excretion in urine.**



Trientine induces urinary copper excretion

Zinc can block intestinal absorption of cu (only in pt without neurological manifestations).

Liver transplantation

Alterations of plasma copper:

2-Copper Deficiency

- **Dietary is rare**
- **Genetic :Menks syndrome**

(Menk's kinky or Steely hair disease)

- **It is a genetic fetal disease (X linked recessive disorder), due to mutation of ATP7A gene**
- **encoding for copper-transport protein which is a trans membrane protein**
- **This gene present in all tissues except liver (very little)**
- **important for regulating Cu transport from small intestine to the blood ,**
- **accumulation of Cu in intestine and kidney**
- **Poor distribution of Cu in other body cells.**

- **Menks syndrome symptoms :**
- **Brittle, kinky, steely, sparse,**
  or tangled hair.
- **Pudgy, rosy cheeks, sagging facial ski**
- **Hypopigmentation.**
- **Feeding difficulties.**
- **Irritability.**
- **Lack of muscle tone, floppiness.**
- **Low body temperature.**
- **Intellectual disability and developmental delay.**
- **Fetal disease**

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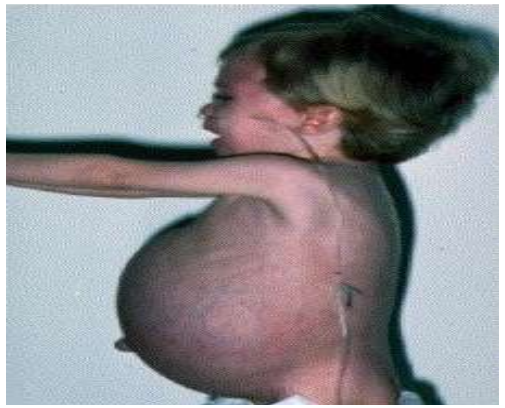
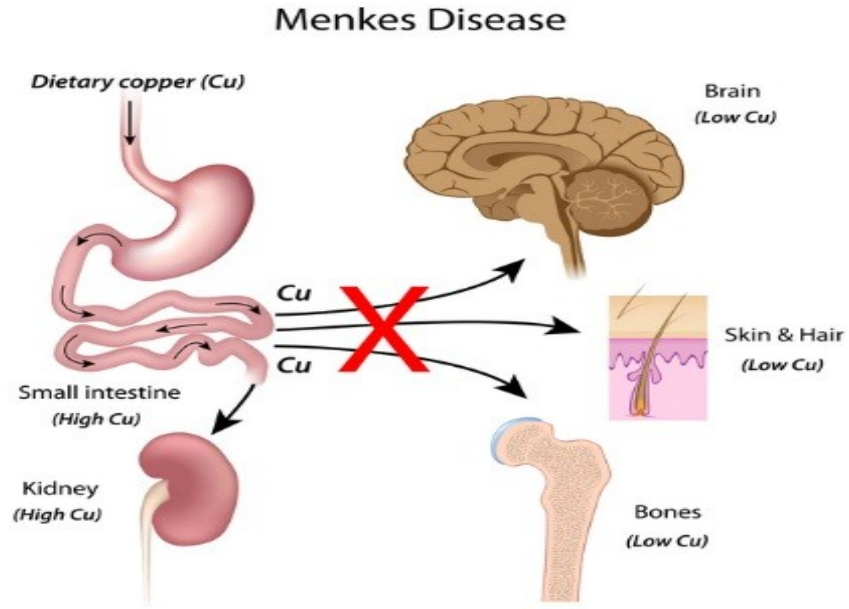
- **OTHER COPPER DISEASES**
- **1. Idiopathic Copper Toxicosis**
- **2. Tyrolian Infantile Cirrhosis**
- **3. Indian Childhood Cirrhosis**





Quiz

- Which is the treatment of Menkes disease ?
  - A. Zinc
  - B. Penicillamine
  - C. Trientine hydrochloride
  - D. Early parenteral copper administration and supportive measures

II-Other Trace elements:

selenium, zinc,

chromium,iodine,floride ,cobalt

2-Selenium

1- is an important antioxidant .

2- It is important for many enzymes as

Glutathione Peroxidase.

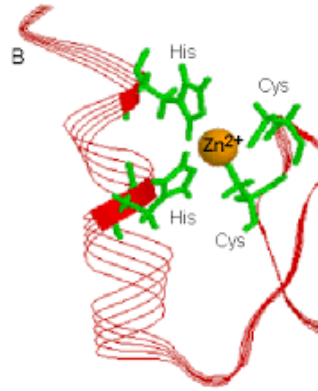
3-Present in 25% of human proteins

Selenocysteine amino acid

3-Zinc

1- It is a cofactor of some enzymes as Alkaline phosphatse & superoxide dismutase.

2-Zn Finger motifs binds to DNA regulating gene expression



3-It is important for storage of insulin

4-wound healing & healthy skin.

5-Strong immune system

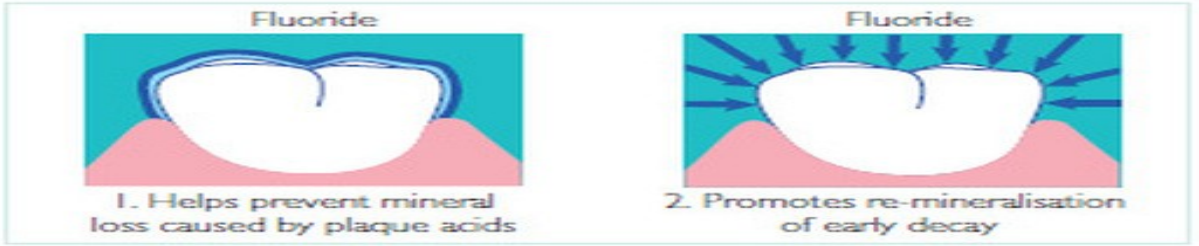
6-Antioxidant nutrient.

7-Healthy hair

4-Fluoride

Present in Drinking water & seafood

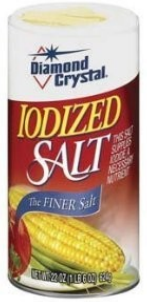
is present in the body almost entirely in bone and teeth.



5-Chromium

- It is an important as a component of glucose tolerance factor (GTF) which is a factor potentiates the effect of insulin by facilitating its binding to the cell receptor.
- Reduce cholesterol & t

6-Iodine



- **Present in: Sea water ,iodized table salt & Sea foods**
- **Enter in the formation of thyroid hormones**
- **Deficiency :excess stimulation of thyroid gland by TSH (Goiter)**

- **7-Cobalt**
- **Component of Vit B_{12} (Methylcobalamin or Adenosylcobalamin)**

- **8-Molybedenum**
- **Essential component of some flavoprotein enzymes as xanthine oxidase and sulfite oxidase which catalyzes the oxidation of sulfite (SO3-) to sulfate (SO4-)**

Minerals act as antioxidants

- Copper
- Manganese
- Zinc
- Iron
- Selenium

Quiz

- Which of the following mineral deficiency may results into impaired growth and development, skin lesions and loss of appetite
- 1- Zinc
- 2- Cobalt
- 3- Magnesium
- 4-chromium

-Selenium is important for the following enzyme:

A) Superoxide dismutase
B) Alkaline phosphatase
C) Glutathione peroxidase
D) catalase

Lecture Summery

- **Inorganic mineral elements** that have a function in the body must be

provided in the diet. When intake is insufficient, deficiency may develop.

- **Wilson's disease (hepatolenticular degeneration).**

Increased serum free cu levels ,Decreased plasma ceruloplasmin,

This disease is characterized by accumulation of large amounts of copper in different tissues

- **Genetic :Menks syndrome**

- **Accumulation of Cu in intestine and kidney ,Poor distribution of Cu in other body cells.**

SUGGESTED TEXTBOOKS

1. Lippincott's Illustrated Reviews in Biochemistry


Thank You